The Bottom Line

Immune Recovery in Pediatric Transplantation: Can T Cell–Depleted Peripheral Blood Stem Cell Transplantation Beat Cord Blood Transplantation?

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The beginning of the 21st century has been a time of change in stem cell transplantation (SCT) practice, particularly in terms of donor selection for pediatric patients. We have witnessed a decline in peripheral blood SCT (PBSCT) in favor of bone marrow (BM) as a donor source, leading to less graft-versus-host disease (GVHD) [1]. With the acquisition of a critical pool of more than 12 million unrelated donors worldwide, this adult stem cell source has achieved some stability in terms of donor availability [2]. However, umbilical cord blood transplantation (CBT) has seen growing acceptance as a ready stem cell source with a low risk for GVHD even with donor–recipient mismatch. The perfection of CBT selection criteria along with concurrent improvements in the quality of cord blood products has produced continuing improvements in transplantation outcomes [3]. Successful new transplantation approaches with related haploidentical SCT promise to again reset the criteria for donor source selection [4]. The article by Oshrine et al [5] in this issue of *The Journal* opens up a further strategy, using partially T cell–depleted (TCD) PBSCT as an alternative to CBT, especially in mismatched SCT.

The study objectives of Oshrine et al's Children's Hospital of Philadelphia group derive from 2 competing problems facing mismatched allogeneic SCT: immune recovery and GVHD. Compared with CBT, PBSCT can transfer immunity to viruses (especially cytomegalovirus) from a seropositive donor, whereas CBT, with only virus-naïve T cells, confers a greater risk of uncontrolled viral reactivation and disease [3]. However, compared with CBT, unmanipulated PBSCT carries an unacceptably high risk of GVHD [1]. These observations set the stage for exploring the option of TCD PBSCT. There is good reason to presume that TCD PBSCT can reduce the risk of GVHD to even below that of unmanipulated BM transplantation, but the ability of TCD PBSCT to establish immune function requires further investigation [6].

In fact, Oshrine et al's study, which compared 55 TCD PBSCTs and 21 CBTs, showed distinct differences in the quality of immune recovery after transplantation. Whereas CD8 T cell recovery was comparable, CD4 recovery was much slower after TCD PBSCT, and was complete only after a second wave of lymphocyte recovery associated with recovering thymopoiesis. Because the anti-CD20 monoclonal antibody rituximab was used in the PBSCTs to prevent Epstein-Barr virus (EBV) lymphoproliferative disease, the recovery of $CD19^+$ B cells was also slower. (The use of rituximab could be considered overkill, given that EBV reactivation has not been reported as a significant problem in TCD PBSCT, and that rituximab carries its own risk of delayed neutropenia [7].) Despite these strategies, the 2 groups demonstrated no difference in T cell mitogen responses or in the need for i.v. immunoglobulin. Most notably, outcomes were highly comparable in the 2 groups, with similar rates of relapse, transplantation-related mortality, and overall survival. However, there was less chronic GVHD with PBSCT, although the difference were not statistically significant. Oshrine et al conclude that partial TCD PBSCT offers a useful alternative to unrelated CBT in pediatric patients. They suggest that a TCR-α/β–positive T cell depletion strategy, currently under evaluation in Europe, could further improve immune recovery by sparing natural killer cells and other accessory cells that are eliminated with the $CD34^+$ selection method [8].

Given the small group size and nonrandomized nature of the study of Oshrine et al, their findings should not be regarded as definitive evidence of the superiority or even equivalence of TCD PBSCT compared with CBT. Nonetheless, their study can be considered a hypothesis-generating study supporting a larger randomized trial comparing CBT with TCD PBSCT. Two issues need to be addressed: the risk of GVHD and the optimum stem cell dose. In terms of GVHD, in the context of partially matched donors, CBT permits greater latitude of mismatch with a lower risk of acute and chronic GVHD compared with unmanipulated BM transplantation or PBSCT; however, more data are needed for TCD PBSCT. In terms of stem cell dose, the lower CD34 cell dose and slower engraftment in CBT are problems that have not yet been entirely overcome by the use of double cord or haploidentical cord transplants or stem cell expansion [9,10]. In contrast, PBSCT uses the optimum stem cell source, with supermassive CD34 cell doses ($>10^6$/kg) regularly achievable, especially in the pediatric population. Over and above overcoming the slow engraftment characteristic of unrelated CBT, such megadoses of CD34 cells should reduce graft rejection, especially in the mismatched setting. Whether such TCD transplants would still retain sufficient numbers of T cells to restore immunity and protect against viral reactivation remains an important unanswered question.

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Although transplantation teams have been very successful in managing the characteristically slow hematologic recovery after CBT, a large comparative study of CBT versus TCD PBSCT might well reveal a significant outcome benefit for the richer stem cell product. Together with the intrinsic opportunities conferred by PBSCT of a continuing source of lymphocytes and stem cells to treat disease relapse and BM failure, such a study could swing the balance away from CBT in favor of TCD PBSCT. We live in a time of rapid advances, however; by the time such a clinical trial is conceived and implemented, related haploidentical SCT may emerge as a key contender to be evaluated against unrelated donor SCT [4].

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Where Are We Going with Autologous Transplantation for Multiple Myeloma?

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High-dose melphalan followed by autologous hematopoietic stem cell transplantation (auto-HSCT) remains an integral component of the treatment of transplantation-eligible patients with multiple myeloma (MM). This treatment is technically not a transplantation, but rather is a rescue from the marrow-toxic effects of melphalan using the patient's own hematopoietic stem cells (HSCs); however, the term "transplantation" is widely used to describe this treatment, and so is used herein.

Melphalan has been dose-intensified to treat plasma cell leukemia and MM [1], but this therapy is limited by prolonged pancytopenia at higher doses of melphalan. Barlogie et al. [2] initially demonstrated the utility of auto-HSCT with bone marrow (BM) grafts, leading to the broad application of auto-HSCT as part of the continuum of initial or later treatment of transplantation-eligible patients with MM. The first use of mobilized peripheral blood (PB) as a stem cell source was reported in 1989 [3] and has led to the use of growth factor (with or without chemotherapy)–mobilized PB as a stem cell source, usually after a high-dose melphalan-based regimen. A phase III study demonstrating the superiority of auto-HSCT over chemotherapy had led to the widespread use of auto-HSCT as part of the initial therapy for transplantation-eligible patients with MM [4]. Terms for the autologous HSCs used for rescue/transplantation include BM, blood or marrow (allowing for the continued use of BM as an abbreviation), PB, HSCs, and hematopoietic progenitor cells (HPCs).

The study of Costa et al. [5] reported in this issue of *Biology of Blood and Marrow Transplantation* demonstrates the increased use of auto-HSCT as part of the initial therapy for transplantation-eligible patients with MM from 1995 to 2010. The study population comprised 20278 patients with MM, 11644 of whom underwent auto-HSCT between 2005 and 2010. Given the formidable challenge of collecting complete data from more than 20000 patients, the investigators conducted a detailed analysis of a subset of 4373 patients with more detailed information. This study further limited eligibility to patients who were within 1 year of MM diagnosis, thus reflecting early and possibly more aggressive disease. This eligibility criterion did not capture those smoldering patients with MM requiring therapy more than 1 year after the initial diagnosis. The cohort likely reflects the majority of symptomatic transplantation-eligible patients with MM, but this is uncertain, owing to the large percentage of patients without Durie-Salmon and International Staging System scores at diagnosis (49% and 39%, respectively). Factors that have changed over time include the increasing use of auto-HSCT in patients aged ≥65 years, the abandonment of most non–melphalan-containing regimens in favor of single-agent melphalan regimens, the increased use of planned tandem auto-HSCT, and the increased use of

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